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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,642	06/18/2001	Denisa D. Wagner	CFBF-P02-004	3076

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/883,642	WAGNER ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-52,61-68,71-73 and 76-79* is/are pending in the application.
4a) Of the above claim(s) ~~*73* is/are~~ withdrawn from consideration. 69, 73, 74, 83, 87

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-52,61-68,71,72 and 76-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of the species 2, that is, "antibodies that inhibit interactions between P-selectin and a ligand for P-selectin and between E-selectin and a ligand for E-selectin", in the Response to Election of Species Requirement, filed 12/13/04, is acknowledged.

Claims 39-52, 61-68, 71, 72 and 76-79 read on the elected species.

Claims 69, 73, 74, 83 and 87 have been withdrawn as being drawn to non-elected species and inventions.

Claims 1-38, 53-60, 70, 75, 80-82, 84-86 and 88 have been canceled previously.

2. For examination purposes, it has been noted that it has been known in the art that PADGEM, GMP-140 and P-selectin are all the same molecule, that is, CD62P.

3. The filing date of the instant claims is deemed to be the filing date of priority application USSN 08/377,798, filed 1/24/95.

Priority application USSN 08/253,663, filed 6/3/94 does not support the instant claims of the instant application.
For example, there is insufficient written description for a "P-selectin antibody for inhibiting an interactions between P-selectin and a ligand for P-selectin and between E-selectin and a ligand for E-selectin".

If applicant desires priority prior to1/24/95; applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 39-52, 61-68, 71, 72 and 76-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies that bind inhibit the interaction between P-selectin and a ligand for P-selectin,
does not reasonably provide enablement for "P-selectin antibodies that inhibit the interaction between P-selectin and a ligand for P-selectin and another selectin, including E-selectin".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

According to Berg (U.S. Patent No. 5,622,701);
The prevalence of non-blocking anti-selectin antibodies suggests that only small regions of the extracellular domain participate directly in binding or influence binding and that most antibodies generated against P- or E- selectin would be expected to generate mainly non-blocking antibodies (see columns2, lines 51-63).
Despite the large number of antibodies isolated to-date against the three selectins, there have been few reports of cross-reacting antibodies that bind to more than one selectin (see column 2, lines 64-66).
No antibody has been isolated that binds to both P- and E-selectin, much less blocks the functions of both of these molecules (See column 3, lines 10-12)

Applicant's reliance on the recitation and enablement of "P-selectin antibodies that inhibit the interaction between P-selectin and a ligand for P-selectin and another selectin, including E-selectin" is derived from page 12, paragraph 2 of the instant specification which discloses:
An agent is also meant to include inhibitors which are not entirely P-selectin specific. For example, an agent may inhibit other selectin interactions in addition to P-selectin inteacitons, e.g. L and/or E selectin interactions. Such overlapping specificity may provide additional therapeutic advantage.

The only "P-selectin antibodies" described by applicant are "P-selectin antibodies" that bind and inhibit P-selectin interactions and not "P-selectin antibodies" that bind and inhibit both P-selectin and E-selectin interactions (see page 9, paragraph 1 of the instant specification).

The present specification fails to provide sufficient disclosure of "how to make" "P-selectin antibodies" that bind and inhibit both P-selectin and E-selectin interactions.

The specification does not appear to account for bispecific antibodies as a possible alternative for cross-reacting "P-selectin antibodies".

The claims and applicant's arguments of record are clearly drawn to cross-reacting P-selectin antibodies that bind and inhibit both P-selectin and E-selectin interactions

Given the propensity for non-blocking anti-selectin antibodies and the absence of cross-reacting anti-selectin antibodies at the time the invention was made, there is insufficient sufficient guidance as to which epitopes or by which procedure the skilled artisan would have been enabled to make cross-reacting anti-selectin antibodies that bound and inhibited both P-selectin and E-selectin interactions.

While some of the inhibitory agents disclosed in the specification as filed may have the properties of inhibiting interactions of multiple selectins,
the specification does not describe nor enable any cross-reacting anti-selectin antibodies that bound and inhibited both P-selectin and E-selectin interactions.

Given the absence of sufficient guidance by the instant specification as to appropriate epitopes or screening procedures, it would have been unpredictable that the skilled artisan would have been enabled to make cross-reacting anti-selectin antibodies that bound and inhibited both P-selectin and E-selectin interactions.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

Without sufficient guidance, making and using "cross-reacting P-selectin antibodies that bind and inhibit both P-selectin and E-selectin interactions" was unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

6. Claims 49 is objected to because "$CD4^{+}$" and "$CD8^{+}$" T cells are the proper designations of these T cell subpopulations and not "CD4", "CD8+" T cells, as currently recited.

Applicant should amend the claims to recite the proper designation of these T cell subpopulations.

7. Claims 39-52, 61-68, 71, 72 and 76-79 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39-52, 61-68, 71, 72 and 76-79 are indefinite in the recitation of an "P-selectin antibody for inhibiting an interactions between P-selectin and a ligand for P-selectin and between E-selectin and a ligand for E-selectin" because the metes and bounds of the "P-selectin antibody" as well as the antibody specificity are ill-defined and ambiguous.

First of all, the claims should indicate that the antibodies are specific for P-selectin, rather than "P-selectin antibody" which does not clearly define the antibody specificity.

In addition, it is not clear whether the antibody binds a P-selectin specific epitope, a common epitope (or common epitopes) between P-selectin and E-selectin and all their ligands, respectively or whether the claims encompass a bispecific antibody that binds both P-selectin and E-selectin, which, in turn, inhibits binding between the selectins and their ligands, respectively.

For example, page 9, paragraph 1 of the instant specification discloses anti-P-selectin antibodies that appear to be P-selectin specific and does not appear to disclose anti-P-selectin antibodies that inhibit P-selectin:P-selectin ligand interactions and E-selectin:E-selectin interactions.

While page 12, paragraph 2 of the instant specification discloses that "an agent is also meant to include inhibitors which are not entirely P-selectin specific. For example, an agent may inhibit other selectin interactions in addition to P-selectin interactions, e.g. L- and/or E-selectin interactions."

However, there is ambiguity as to what is meant by "not entirely P-selectin specific" and what is the actual specificity of the claimed "P-selectin antibodies" as they read on "inhibiting an interactions between P-selectin and a ligand for P-selectin and between E-selectin and a ligand for E-selectin".

For example, it is unclear whether the claimed "P-selectin antibodies bind specific epitopes directly associated with the "inhibition of interactions between P-selectin and a ligand for P-selectin and between E-selectin and a ligand for E-selectin" or the claimed "P-selectin antibodies" inhibit the selectin interactions, particularly the E-selectin:E-selecin ligand interactions via indirect mechanisms.

The metes and bounds of the claimed "P-selectin antibodies" are ill-defined and ambiguous.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

8. Upon reconsideration of applicant's arguments set forth in the Brief, filed 5/18/04, in conjunction with applicant's election of "P-selectin antibody for inhibiting an interactions between P-selectin and a ligand for P-selectin and between E-selectin and a ligand for E-selectin" because the metes and bounds of the "P-selectin antibody",

the previous rejections under 35 U.S.C. § 102(b) as being anticipated by Furie et al. (EP 0496832); Palabrica et al. (WO 93/06863) (1449; #AU) ; and McEver et al. (U.S. Patent No. 5,378,464) have been withdrawn.

9. Claims 39-52, 61-68, 71, 72 and 76-79 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Furie et al. (EP 0496832) (1449; #AQ) AND/OR Palabrica et al. (WO 93/06863) (1449; #AU) AND/OR McEver et al. (U.S. Patent No. 5,378,464) in view of the art known use of combination therapies in the treatment of atherosclerosis, as taught by Coller et al. (U.S. Patent No. 5,976,532) (1449; #AO) in view of the art known underlying lesions of atherosclerosis and known treatments of atherosclerosis as acknowledged in the Background of the Invention on pages 1-2 of the instant specification and in view of the art known modes of administration practiced by the ordinary artisan at the time the invention was made, as acknowledged on pages 12-16 of the instant specification for the reasons of record and further in view of newly added Berg (U.S. Patent No. 5,622,701).

Upon reconsideration of applicant's elected species drawn to the use of a "P-selectin antibody for inhibiting an interactions between P-selectin and a ligand for P-selectin and between E-selectin and a ligand for E-selectin",

Berg has been added to address this claimed antibody specificity as it reads on antagonistic antibodies that bind an epitope(s) common to both P-selectin and E-selectin.

Berg teaches antagonistic antibodies, including bispecific antibodies, that bind to P-selectin and E-selectin and are able to block the inflammatory events mediated by P-selectin and E-selectin-mediated interactions (see Antibodies of the Invention on columns 5-13), which are suitable for inhibiting inflammatory or thrombotic conditions, including therapeutic and prophylactic treatment of ischemia-reperfusion injury, myocardial infarction and cardiac surgery (e.g., see column 8, paragraph 2; column 16, paragraph 1; column 17, paragraph 2; and Claims) (see the entire document, including Summary of the Invention, Description of the Preferred Embodiment and Claims).

In addition, Berg is consistent with the prior art in teaching therapeutic and prophylactic pharmaceutical compositions, dosages and modes of administration, including combination therapy in amounts to achieve a cure or at least partially arrest the disease or condition, which will depend upon the severity of the disease and the condition of the patients (see columns 16-18).

As indicated previously, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosures of Furie et al., Palabrica et al. and McEver et al.

Furie et al., Palabrica et al. and McEver et al. each differ from the claimed methods in differences in their explicit teaching of all of the underlying cells and ligands associated with P-selectin-mediated binding, adhesion and activation. Given the combined teachings of P-selectin-mediated events, the claimed limitations encompassing cell types, ligands (e.g. see claims 42-52), the inhibitory properties of the claimed agent (e.g. see claims 60-61), the effects on atherosclerotic lesions (e.g. see claim 62-65) would be intrinsic or expected properties of the referenced methods of inhibiting atherosclerosis with anti-PADGEM or anti-GMP-140 antibodies. Furthermore, the combined teachings of Furie et al., Palabrica et al. and McEver et al. provide for the various cell types and interactions associated with P-selectin mediated events.

Further, Berg reviews the properties, expression and interactions of P-selectin and E-selectin known to the ordinary artisan at the time the invention was made (see Background of the Invention on columns 1-2).

Further, Berg teaches cross-reacting antibodies might be capable of aborting the inflammatory process at more than one level thereby providing more broadly useful therapeutic agents for inflammatory conditions than antibodies specific for a single selectin (see columns 2-3, overlapping paragraph).

Furie et al., Palabrica et al. and McEver et al. differ from the claimed methods in differences in their explicit teaching of the known underlying lesions in atherosclerosis and in the known use of cardiovascular interventions and surgery to treat atherosclerosis at the time the invention was made. The Background of the Invention acknowledges the art known underlying lesions of atherosclerosis and known treatments of atherosclerosis at the time the invention was made. In addition to the teachings of Furie et al., Palabrica et al. and McEver et al. to treat atherosclerosis with anti-GMP-140 / anti-PADGEM antibodies, Palabrica et al. teach the use of such antibodies to inhibit vascular narrowing in the context of the known cardiovascular procedures associated with the treatment of atherosclerosis at the time the invention was made.

As indicated above, Berg similarly teaches antibodies suitable for inhibiting inflammatory or thrombotic conditions, including therapeutic and prophylactic treatment of ischemia-reperfusion injury, cardiac surgery such as angioplasty (e.g., see column 8, paragraph 2; column 16, paragraph 1; column 17, paragraph 2; and Claims).

One of ordinary skill in the art at the time the invention was made would have been motivated to select or to modify the teachings of Furie et al., Palabrica et al. and McEver et al. to treat atherosclerotic patients with P-selectin-specific antibodies with the cross-reacting antibodies taught by Berg due to the advantages of antibodies that bind to both P-selectin and E-selectin so as to block the capacity of both these molecules to participate in adhesion receptors and counter-receptors (e.g. see column 2, paragraph 2 – column 3, paragraph 1 of Berg).

A person of ordinary skill in the art would have recognized that the cross-reacting antibodies described by Beg would be interchangeable and advantageous with the anti-P-selectin antibodies taught by the primary references in the treatment of atherosclerotic patients, including those undergoing vessel-corrective surgery.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosures of Furie et al., Palabrica et al. and McEver et al.

The claimed limitations encompassing cell types, ligands (e.g. see claims 42-52), the inhibitory properties of the claimed agent (e.g. see claim-61), the effects on atherosclerotic lesions (e.g. see claim 62-65) would be intrinsic or expected properties of the referenced methods of treating atherosclerosis with cross-reacting antibodies that inhibit interactions between P-selectin and a ligand for P-selectin and between E-selectin and a ligand for E-selectin, as taught by Berg.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant arguments and the examiner's rebuttal are essentially the same of record with respect to issues other than that associated with the elected species as "antibodies that inhibit interactions between P-selectin and a ligand for P-selectin and between E-selectin and a ligand for E-selectin".

See the previous Office Actions for a more complete analysis of applicant's arguments and the examiner's rebuttal concerning the rerferences already of record.

Applicant has argued that the deficiencies of the primary references with respect to the inhibition of P-selectin, E-selectin and L-selectin and their ligands with anti-P-selectin antibodies is not cured by the teachings of Coller et al.

Applicant's arguments of record do not address the teachings of the newly added Berg reference.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300

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Phillip Gambel, PhD.
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March 17, 2005

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